CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89884

CORRESPONDENCE

ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Hercon Laboratories Corporation
Attention: Joseph J. Sobecki
P.O. Box 786
York, PA 17405

JUN 14 1995

Dear Sir:

This is in reference to your abbreviated new drug applications dated November 12, 1987, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nitroglycerin Transdermal Delivery Systems.

Reference is also made to your amendments dated April 29, and December 8, 1994.

The applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding drug substance:

DMF as amended remains inadequate. A separate letter outlining the remaining deficiencies has been issued to the DMF holder.

2. Regarding manufacturing and processing:

3. Regarding laboratory controls:

4. Regarding method validation:

B. Labeling Deficiencies

General Comments:

a. Delete the terminal zero following a decimal point when expressing the size of the system.

b. We have concerns about the extremely similar labeling between these unapproved applications and your pending supplemental applications for We believe that such similarity in the labeling for these two inequivalent

products will pose a selection problem for substitution by the pharmacist. Please comment and/or revise accordingly.

c. In accord with 21 CFR 201.57(f)(2), make the following revision to your professional package insert.

Reprint the patient information brochure at the end of the professional package insert, (i.e., following the HOW SUPPLIED section).

Container: 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr

Pouch

1. We encourage you to differentiate between your different product strengths by using boxing and/or contrasting colors.

2. Front panel

Revise as follows:

a. Prominently display the size of the system in parenthesis. For example:

0.4 mg/hr
(___ cm^2)

b. Each ___ cm^2 contains ___ mg of nitroglycerin ...

c. APPROXIMATE RATED RELEASE *IN VIVO* ___ mg/hr

Immediate patch - Satisfactory

Carton: 30's

1. **Front Panel**

See comments under Container (Pouch).

2. **Left Side Panel**

Usual Dosage -

... of 10 to 12 hours; unless otherwise directed by your physician.

3. Right Side Panel

   a. Add the following to the storage instructions; as seen in your insert labeling and by the innovator:

      Do not refrigerate

   b. We note that you have not included any pictorials, as does the innovator, which would aid in the safe use of this product. Please include.

Patient Package Insert:

1. We note you have not included a copy of the diagrams which are to appear in the Patient Package Insert, please comment.

2. Patient Instructions #1 -

   Add the following as the first sentence.

   Each Nitroglycerin Transdermal System is individually sealed in a protective package. Open the ...

3. Patient Instructions # 4 -

   Revise as follows:

   ... the backing (which is still in place) to avoid touching the sticky side of the patch.

4. Add the following to the storage recommendations:

   Do not store the patch outside the individual package. Apply patch immediately upon removal from the protective package.

Insert:

1. Delete "Prescribing Information" found above the "DESCRIPTION" section heading.

2. DESCRIPTION

   a. Paragraph 3 -

      ... has delivered approximately ...

   b. We note, you have indicated that your nitroglycerin transdermal system contains the nitroglycerin in a laminated polymer matrix. This

is not consistent with the statement on your carton labeling, which indicates that the nitroglycerin is contained in a polymer adhesive. Please revise the physical description and the inactive ingredients accordingly.

3. WARNINGS

Paragraph 2 -

... harmless in itself, but ...

4. PRECAUTIONS

a. General

Paragraph 5 -

... patients had decreased exercise tolerance ...

b. Information for Patients

In accord with 21 CFR 201.57(f)(2), revise this subsection as follows:

Add as the last sentence, "See Patient Information at the end of insert".

c. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Combine the second and third paragraphs into one paragraph.

d. Pediatric Use

... in pediatric patients have not ...

5. ADVERSE REACTIONS

a. Relocate the third paragraph "Allergic reactions... ", to be the second paragraph of this section.

b. Revise the paragraph referring to "methemoglobinemia" to read as follows:

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion

of its diagnosis and treatment is deferred (see OVERDOSAGE).

[NOTE: This is the third paragraph in this section].

c. Relocate the last paragraph, "Application-site irritation ...", to be fourth paragraph of this section.

6. HOW SUPPLIED

Please add a description of the transdermal patches, including any direct on-patch printing.

Please revise your container labels, carton and insert labeling and then prepare and submit in final print.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Please confirm that the drug product expiry dating will be calculated based on the date of manufacture of the original laminate and not on the date of manufacture of the split laminate or the die-cutting of the patches.

2. Please be advised that storage of the original or split laminate for the proposed maximum six month interval is contingent upon (1) above.

The file on these applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the applications. Your amendments should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered MAJOR amendments and should be so designated in your cover letters.

You will be notified in a separate letter of any deficiencies in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 6/14/95

Florence S. Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #89-884, 89-885, 89-886
DUP Jacket
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-647/SBasaran/4-10-95/6-1-95 S. Basaran 6/14/95
HFD-647/JSimmons/4-21-95 6.14.95
HFD-613/JWhite/5-12-95
HFD-617/TAmes/4-24-95 6/14/95
89884N03.LSB/disc#5
F/T by pah/5-24-95

TYPE OF LETTER: Not Approvable/Major Amendment

61
Litwack

ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Hercon Laboratories Corporation
Attention: Joseph J. Sobecki, R.A.C.
P.O. Box 786
York, PA 17405

MAR 29 1996

Dear Sir:

This is in reference to your abbreviated new drug applications dated November 12, 1987, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nitroglycerin Transdermal Delivery Systems.

Reference is also made to your amendments dated August 7, 1995.

The applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

The individual unit specifications for in-process control of the bulk lamination are not consistent with your final drug product specifications or with USP specifications for transdermal patches. Please revise your in-process specifications to be consistent with your final drug product specifications and compendial requirements.

B. Labeling Deficiencies

Container Labels:

Pouch - Satisfactory as of 8-7-95 submission.

Immediate Patch - Satisfactory as of 12-8-94 submission.

Carton Labeling: (30s)

Satisfactory as of 8-7-95 submission.

Professional Package Insert Labeling:

1. DESCRIPTION

a. Revise the last sentence of the third paragraph to read: ...delivered approximately 7% of...

b. List the imprinting ink which is used on the patch.

2. PRECAUTIONS

a. Carcinogenesis, Mutagenesis, Impairment of Fertility.

i. Delete the "and" from the subsection title.

ii. Delete the penultimate sentence of the second paragraph (Incidences...females).

b. Revise the subsection title as follows:

Pregnancy: Pregnancy Category C:

Patient Package Insert Labeling:

Satisfactory as of 8-7-95 submission.

Please revise your container labels, carton and insert labeling and then prepare and submit in final print. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug of the application prior to approval.

The file on these applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the applications. Your amendments should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered MAJOR amendments and should be so designated in your cover letters. You have been notified in a separate letter of any deficiencies in the bioequivalence portion of your application. Please be advised that you must submit as amendments to your original applications any changes in the chemistry, manufacturing and controls sections of your applications or batch records for any additional lots of

drug product manufactured in response to the deficiencies cited for the bioequivalency portion of your applications. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/29/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 89-886

APR 25 1988

Hercon Laboratories Corporation
Attention: Agis F. Kydonieus, Ph.D.
200 B Corporate Court
South Plainfield, NJ 07080

Dear Sir:

Please refer to your abbreviated new drug application dated November 13, 1987, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Transdermal System, 15 mg/24 hour.

Reference is made to your communications dated December 4, 1987, March 10 and 11, 1988 and to our letter of February 17, 1988.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

I. Labeling has been reviewed. In this regard:

COMMENTS:

Individual patch (direct patch and adhesive backing)

Direct patch (protective covering): delete the word

Adhesive backing label: Add the word "transdermal" after nitroglycerin. You may shorten the address to create additional space if necessary.

Carton - Satisfactory

Patient package insert

In the "Special Advice" section please make a comment [redacted] can be worn in the bath, in shower or while [redacted].

Insert - professional

Delete the decimal point from 125 mg in the DESCRIPTION section.

In the CLINICAL PHARMACOLOGY section:

Replace the word ' with "resultant" in paragraph one.

The INDICATIONS section should be boxed.

It is recommended that you revise your individual patient, carton and insert labeling, then prepare and submit draft labeling for our review and comment.

II. It is acknowledged that you will address other comments in our letter referenced above when information becomes available.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/25/88

Harold Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFN-233
JBacsanyi/JLMeyer/BHa
r/d JLMeyer/HSeife
ved 4/21/88 (3676v)
Not Approvable

BHA 4/21/88
JBacsanyi 4/21/88
JLMeyer 4/22/88

ANDA 89-886

Hercon Laboratories Corporation
Attention: Agfa F. [redacted], Ph.D.
200 B Corporate Court
South Plainfield, NJ 07080

Dear Sir:

FEB 17 1988

Please refer to your abbreviated new drug application dated November 13, 1987, submitted pursuant to Section 508 of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Transdermal System, 15 mg/24 hours.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

I. Labeling has been reviewed, in this regard:

COMMENTS:

General: Numbers are not to be a part of the trade name. Such numbers have been shown to contribute to confusion and dispensing errors. The trade name "NTS" is presently used by Bolar, therefore Hercon must select another trade name.

Direct Patch Label : Not Satisfactory

Delete numeral from the brand name. Add the word "transdermal", also the address of the company (city, state, zipcode).

There is no labeling submitted for the adhesive foam pad (which will show when the patch is on the patient).

Carton: "Generic" labeling submitted.

Delete numeral from the brand name - Reverse the Fahrenheit and Celsius designations in the storage directions.

Patient package insert:

Modeled after the Nitrodisc (Searle) patient package insert. Reverse the Fahrenheit and Celsius designations in the storage recommendations. Add the name and address of the manufacturer, and date of issue to the bottom of the insert.

Professional Insert:

Key's insert is used as a model -
Storage conditions should follow the HOW SUPPLIED section.
Will check with bio about the blood levels in the bio-study.

We recommend that you revise direct patch, carton and insert labeling and submit draft labeling for the adhesive foam pad, that is, the information which will show when the foam pad is on the skin. Final printed labeling cannot be approved until firm selects another trade name.

II. It [illegible] to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity. In this regard:

1. It is noted that photo copies of application to market a New Drug For Human Use, Form FDA 356h were used. It is recommended that you use only the original form for the application.

2. In regard to the manufacture of Nitroglycerin/Plastisol Mixture by( )

   A. Submit bulk labels used in transferring the base liquid polymer from Hercon to and active liquid polymer from( ) back to Hercon and container/closure system to assure the proper identity, strength and quality of the raw material.

      Please note reference to an existing drug master file is discouraged.

3. Tests and specifications of your finished dosage form indicated the assay of nitroglycerin at (80% to 120%), higher than the range normally specified in USP. Please clarify.

4. A referral from( ) was dated August 2, 1984. It is suggested that a copy with recent date be submitted.

5. Pages 61 to 74 of your submission are missing, please clarify.

III. In regard to your stability study:

1. It is recommended that accelerated stability study with product specific to this application, i.e. transdermal system with [illegible] be conducted and submitted for review.

2. It is recommended that tests and specification for content uniformity to include RSD as an additional criteria for your finished product control.

3. Submit test results (and chromatogram) to show that ( ) in house method is stability indicating.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

Enclosure: Form 356h (3 copies)

cc:
HFN-233
JBacsanyi/JMeyer/BHo/trc/2/12/88
2126m pages 19-21
Not Approvable
JMeyer 2/16/88

FEB 17 1988

ANDA 89-884 (5 mg/24 h)
89-885 (10 mg/24 h)
89-886 (15 mg/24 h)

Hercon Laboratories Corp.
Attention: Agia F. Kydonieus, Ph.D.
200B Corporate Center
So. Plainfield, NJ 07080

Dear Sir:

Reference is made to the skin irritation study you submitted on November 12, 1987 for Nitroglycerin Transdermal Systems.

The study has been reviewed by the Division of Anti-Infective Drug Products, HFN-180. However, before they can make their final decision you should provide a detailed explaination concerning the patient who experienced sensitization to the product.

Please let us have your response promptly.

Sincerely yours,

/S/ for

2-17-88

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFN-232
RPollock/BHo 2/16/88
kl/2-16-88/1297n
letters

ANDA 89-004

Hercon Laboratories Corporation
Attention: Agis F. Kydonieus, Ph.D.
200B Corporate Court
Middlesex Business Center
So. Plainfield, NJ 07080

DEC 8 1987

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Nitroglycerin Transdermal System, 15 mg/24h

DATE OF APPLICATION: November 12, 1987

DATE OF RECEIPT: November 16, 1987

We will correspond with you further after we have had the opportunity to review the application.

You must cite the September 15, 1978 Federal Register Notice (VOL 43, NO 180) as the reference drug.

Please revise your labeling certification statement to indicate that your labeling will comply with the appropriate Federal Register Notice requirements and is patterned after a similar conditionally approved product.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

/S/ 12/8/87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc: JMeyer 12/7/87
DUP HFN-230
Rosen/Meyer
kl/12-04-87
Ack 1171b

ANDA: 89-884 (5 mg/24 hrs)
89-885 (10 mg/24 hrs)
89-886

Hercon Laboratories Corp.
Attention: Agis F. Kydonieus, Ph.D.
200 B. Corporate Court
South Plainfield, NJ 07080

MAY 18 1988

Dear Dr. Kydonieus:

Reference is made to your abbreviated new drug applications for Nitroglycerin Transdermal Systems.

This letter is to inform you of the recommendations pursuant to a recent meeting of The Center's Labeling and Nomenclature Committee and others from the Center. The topic at the meeting was the reconsideration of information required to appear on the patch of a transdermal system when the system is on the patient.

The group concluded that the established name of the active ingredient and strength (potency) would be the only items required.

Additional information: proprietary name, transdermal, firm name, place of business, are now optional.

We trust this information to be useful in your planning and execution of patch labeling in the future.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-238
HFD-83
JBacsanyi/je/5-13-88
fyi
7840A/ pg 8

ANDA [redacted]

AUG 31 1988

[redacted]
Attention: [redacted]
200 E Corporate Court
South Plainfield, NJ 07080

Dear Madam:

Please refer to your abbreviated new drug application dated November 13, 1987 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Transdermal System, 15 mg/24 hours.

Reference is made to your communication dated May 17, 1988 and to our letter of February 17, 1988.

The application is deficient and therefore not approvable under Section [redacted] of the Act for the following reasons:

I. Labeling has been reviewed. In this regard:

Individual patch (Direct patch and adhesive backing):

Direct patch (protective covering):

Satisfactory, however, you may wish to consider our letter of May 18, 1988. We are concerned about the amount of information you propose to display in a small area.

Adhesive backing Label:

Delete the letter "s" in 24 hrs, otherwise satisfactory.

Cartons: Satisfactory

[redacted] Inserts: Satisfactory

[redacted] Inserts:

[redacted] words "1 hour" with "1/2 hour" in sentence [redacted] paragraph two of the CLINICAL PHARMACOLOGY section.

It is recommended that you submit draft labels for the individual patch, and final printed labeling for the cartons, patient package insert and professional insert.

II. It is acknowledged that other comments in our letter referenced above are being addressed and a response will be forwarded upon availability.

The file is now closed. We are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/31/88

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-233
JBacsanyi/JLMeyer/EMo BB 8/30/88
r/d JLMeyer/MSeife
ved 8/25/88 (4111v)
Not Approvable Bacsanyi (8-30-88)
JLMeyer 8/30/88

ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

OCT 29 1993

Hercon Laboratories Corporation
Attention: Joseph J. Sobecki
P.O. Box 786
York, PA 17405

Dear Sir:

This is in reference to your abbreviated new drug applications dated November 12, 1987, submitted pursuant to Section 505(j) of the Food Drug and Cosmetic Act, for Nitroglycerin Transdermal Delivery Systems.

Reference is also made to your amendments dated April 27, 1993.

The applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

2. Regarding other ingredients:

a. Please provide DMF authorization letters for acrylic polymers

b. Solid acrylic polymer should be included in the other ingredients section.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

4. Regarding container/closures:

   a. Please provide data that nitroglycerin does not migrate or penetrate into the liner, which covers the adhesive surface of the patch.

   b. Water vapor transmission testing per <671> USP XXII for 304 and 302 packaging film should be performed to verify that the pouch is impermeable to water vapor.

   c. Please provide supplier COAs for silicone treated liner.

   d. Please provide the physicochemical tests for packaging film (302 and 304) per <661> USP XXII/NF XVII.

   e. Please provide the vacuum leak test to verify that the pouches are properly sealed.

5. Regarding laboratory controls:

   a. Regarding in-process QC test results, please define

   b. testing should be included in your in-process testing.

   c. Please provide residual solvent limits for each solvent employed in the formulation/process.

   d. In regard to solvent residues is the 1000 ppm limit based on total patch weight? Please specify.

   e. We note that the residual solvent found in the finished product is less than 50 ppm while the limit is not more than 1000 ppm. Please submit lower the limits based on more reasonable estimates.

f. Please provide percentage of patch content limits for dissolution.

g. Please provide chromatographic purity limits and degradation products test and limits in your finished product and stability testing protocol.

h. Please submit correlation data between the in vitro release rate and in vivo drug delivery.

i. Material balance of the drug released and drug retained in the patch should be reconciled.

6. Regarding the adhesive:

a. Please comment on the effects of perspiration and bathing on the adhesion of the patch.

b. Please provide data characterizing the ageing effect on the patch adhesive.

7. Regarding method validation:

8. Regarding stability:

a. Please describe your sampling plan for stability testing. We recommend that at least two containers be sampled for each sampling period. Please refer to CDER Stability Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, February 1987.

b. In your stability protocol and reports, the degradation products and their limits should be included.

c. Regarding stability data for the laminate.

i. Please describe the packaging and storage of the roll stock products.

ii. Under what conditions and how long will the roll stocks be stored before cutting into patches?

B. Labeling Deficiencies

COMMENTS:

General Comments:

1. We note that when the different strengths are compared side to side they are barely discernible. This issue concerns us. We believe these products could easily be confused and could lead to dispensing errors. Please comment on how you are going to differentiate your products.

2. We refer you to 21 CFR 314.94(a)(8)(ii) which clearly defines the quantities of draft or final printed labeling to be submitted.

Foil Pouch:

We ask that you include a revision date or other identifying mark.

Carton: 30 count

1. Federal caution statement, ...DISPENSING WITHOUT PRESCRIPTION. (please delete).

2. We ask that you include a revision date or other identifying mark.

Patient Package Insert:

Please revise your patient package insert to be in accord with the patient package insert of Transderm-Nitro by Ciba revised 6/89 and approved December 1, 1989, then submit draft copy.

Insert:

DESCRIPTION

In accordance with good pharmaceutical practice, all dosage forms should be labeled to state all inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond by noting the inactive

ingredients present in these products. This can be done in an "Each system contains:..." statement.

INDICATIONS AND USAGE

This entire section should be revised to be in accord with the Federal Register notice of July 15, 1993 as follows:

> Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

ADVERSE REACTIONS

1. Paragraph 2, ...and treatment see **OVERDOSAGE**. (please note that **"OVERDOSAGE"** should be in bold capitalized print).

2. Please include the following as a new paragraph between current paragraph 4 and 5:

Application-site irritation may occur but is rarely severe.

OVERDOSAGE

Last paragraph, ...blue, 1 to 2 mg/kg... (note "to" rather than a hyphen).

DOSAGE AND ADMINISTRATION

Paragraph 1, penultimate sentence, ...is sufficient (see **CLINICAL PHARMACOLOGY**). (note: **"CLINICAL PHARMACOLOGY"** should be in bold capitalized print).

Please revise your labels and labeling, then prepare and submit draft copy for our review and comment.

In addition to responding to these deficiencies, please note that samples will be picked up by an FDA representative for methods validation.

The file on these applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The

responses to this letter will be considered MAJOR amendments and should be so designated in your cover letters. You will be notified in a separate letter of any deficiencies in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 10/29/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

★ SEE ANDA 89884, 89885 FOR BIO REV.

ANDAs 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

MAY 30 1997

Hercon Laboratories Inc.
Attention: Robert M. Pilson, R.Ph., J.D.
P.O. BOX 786
York PA 17405

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on October 10, 1996 and the amendment dated November 22, 1996, for Nitroglycerin Transdermal Delivery Systems 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr.

The Office of Generic Drugs has reviewed the bioequivalence data submitted. The *in-vivo* bioequivalence study conducted has been found unacceptable and the following comments are provided for your consideration:

1. There is no evidence of gender-by-treatment interaction ($p > 0.43$) for all parameters and analytes in the original study.

2. There is some evidence ($p < 0.10$) of group-by-treatment interaction for parent compound lauct (log area under the curve 0-t) and laucinf (log area under the curve 0-infinity). However, the way the study was conducted, with the start of the second group beginning only a week after the finish of the first group, and with the assay of the blood samples taking place after both groups were completed, raises the question of whether group-by-treatment interaction was a realistic possibility.

3. In the original study, if the mean plasma levels of the test and reference products at each time point for the parent compound, 1,2 metabolite and 1,3 metabolite are compared, a general trend of lower drug levels with the test in comparison with the reference is observed. This trend is much more prominent in the case of the 1,3 metabolite. The same trend still exists even when the data of subject #121 is removed from the mean data set of 36 subjects. Thus, the data of subject #121 is intensifying this effect rather than behaving as an outlier.

4. Being that no other subjects were retested besides #121, it is not possible to carry out a formal statistical test to verify that the relative performance of T and R was consistent between studies for the other subjects but inconsistent for subject #121. Under certain assumptions, we may conclude that the T/R ratio seen in subject #121 in the original study was statistically significantly lower than the T/R ratio seen in subject #121 in the retest (for lauct and laucinf of the 1,3 metabolite). However, this does not answer the question of why it was lower.

5. Furthermore, the products tested (both test and reference) in the retest were different lot numbers than the products tested in the original study.

6. The interesting feature of the test product profiles from the original study is that the levels of the 1,3 metabolite begin to decline after the 8 hour sample, going below the limit of detection around 14 hours. The levels of the 1,2 metabolite and the parent compound also drop markedly after the 8 hour sample. This pattern is not seen in either of the test product profiles in the retest, nor was it seen in the profiles for the reference product. What could have caused such a profile in the original study? Could it represent a product failure? If it represents a product failure, since it was seen with the test product, does it have implications for the equivalence of the products? Could it have been due to some characteristic of subject #121? If so, why was it not seen in the retest? Was it because a different lot number was used in the retest?

7. In recent years, the Agency has adopted the use of logarithmic transformation for AUC and C_{max} data of the bioequivalence studies. There is no evidence based on scientific data that the use of the log transformation for AUC and C_{max} from orally administered dosage forms does not apply to nitroglycerin transdermal patches. Hence, in the absence of such evidence, data from 36 subjects is insufficient to make a judgment as to whether the assumptions underlying the current statistical bioequivalence analyses are better met by the untransformed parameters rather than the log-transformed parameters, for the original study.

8. The request for a waiver of *in-vivo* bioequivalence studies for your 0.2 mg/hr and 0.6 mg/hr nitroglycerin transdermal products will not be considered until an acceptable bioequivalence study is conducted on your 0.4 mg/hr Nitroglycerin Transdermal System.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/ 5/30/97

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.1

ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-886 (0.6 mg/hr)

Hercon Laboratories Corporation
Attention: Joseph J. Sobecki, R.A.C.
P.O. BOX 786
York, PA 17405

AUG 18 1994

Dear Mr. Sobecki:

This is in reference to your abbreviated new drug applications dated November 12, 1987, submitted pursuant to Section 505(j) of the Food Drug and Cosmetic Act, for Nitroglycerin Transdermal Systems.

Reference is also made to your amendments dated April 27, 1993 and April 29, 1994.

These applications are deficient and, therefore, not approvable under section 505 of the Act for the following reasons:

The Division of Bioequivalence has determined that the bioequivalence study is unacceptable under 21 CFR §314.127(a)(6)(i), for the following reasons:

1. BIOEQUIVALENCE STUDY

   a. For nitroglycerin, the 90% Log transformed confidence intervals for both C_{max} and AUC were outside the acceptable range of 80-125%. [Hercon versus Transderm-Nitro: LN(Cmax), % and LN(AUC0-24), %, Hercon versus Key: LN(C_{max}), % and LN(AUC0-24), %.] The AUC values for 1,2-dinitroglycerin, Hercon versus Key, were also outside the acceptable range of 80-125%.

   b. There is a discrepancy in the number of data set reported in the mean data and the data used in the statistical analysis (ANOVA). In the future submission, you are advised to report the results only from subjects who completed both test and reference products.

   c. The data reported in the mean data calculation and in the variance analysis (ANOVA) are inconsistent. In the mean data calculation (see pages 306-308,

of your April 27, 1993 submission), those samples with assayed values less than the limit of quantitation (LOQ) were apparently treated as "missing" (see the count, N, in the mean data). During the procedure of ANOVA, those samples with assayed values less than LOQ were reported as "zero". In the future submission, you are advised to be consistent in the data presentation and to report those values less than LOQ as zero.

d. You described (on page 351, of your April 27, 1993 submission) how the time to steady state was determined. Criterion 1 (requires no significant differences among the concentrations observed at each time point prior to the steady state time) appears to be in error. Please describe how this would affect the values of C_{max}, C_{min}, C_{av}, and the value of degree of fluctuation (DF). Since this information is not considered to be the primary parameters for bioequivalence, at the present time the error in the determination of time to steady state is considered, not to affect the conclusion of the study.

e. The batch size of the test product was not reported.

f. The residual content of nitroglycerin in the used patches was determined but not submitted.

g. It should be noted that each test patch was applied for 24 hours, which is different from the dosing schedule (i.e., to include a daily patch-off period of 10-12 hours) specified in the labeling of this drug product. In the future submission you are advised to apply the patch for 12-14 hours. Please be advised that an IND may be required for outside labeling use.

h. The drug release data were derived from 6 dosage units. You are advised that in vitro dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range, and coefficient of variation data.

2. WEAR AND REPEATED INSULT PATCH TEST

a. Eighty-six (86) subjects completed the induction phase of the study. According to the study protocol, each subject received 24-hour patch applications three times a week (on Monday, Wednesday, and Friday) for three weeks and for

each patch application the sites were scored at 24-hour and 48-hour. The irritation scores at 24-hour and 48-hour showed a total number of eighty six. Please clarify whether the scores reported were mean values. If those were mean values then you should report the mean, range, and coefficient of variation of the data as well.

b. There is a discrepancy in the number of data set (i.e., N) reported in the challenged phase. You should clarify why N for the 48-hour score is more than that of the 24-hour score.

c. The bioequivalence study on 0.4 mg/hr patch was conducted while the wear and repeated insult patch study was conducted on 0.2 mg/hr patch. The observation made on the wear properties and the irritation potential of this study pertains only to the 0.2 mg/hr patch and the study does not establish that the larger patches have acceptable skin irritation characteristics.

Based upon the deficiencies outlined above, it is the opinion of the Division of Bioequivalence, that a new in vivo bioequivalence study will be needed to support the approval of these abbreviated new drug applications.

The Office of Generic Drugs will suspend any further review of these applications until an amendment containing complete information and data necessary to support your chosen plan of action is submitted to the Agency.

The file is now closed. You are required to take an action described under 21 CFR §314.120 and 21 CFR §314.96 which will either amend or withdraw these applications. **Your amendment(s) should respond to all cited chemistry, labeling and bioequivalence deficiencies stated above and/or to those presented in previous letters.** In the event that reformulation of your product is needed to meet the agency's bioequivalence requirements, revised chemistry, manufacturing, controls and labeling information should also be included in the amendment. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. **Your response to this letter will be considered as a Major Amendment and should be so designated in your cover letter. The cover letter should clearly state what amendments are contained in the submission (i.e., Bioequivalence, Chemistry, Labeling).** If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Representatives of the Division of Bioequivalence are available to discuss this letter and assist you. Please contact Jason A. Gross, Pharm. D., at (301) 594-2290 for further assistance.

Sincerely yours,

/S/ 8/17/94

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDAs 89-884 0.2 mg/hr
89-885 0.4 mg/hr
[redacted]
BIO 96-018B

Food and Drug Administration
Rockville MD 20857

JUN 25 1996

Hercon Laboratories Corporation
Attention: Joseph Sobecki, R.A.C.
P.O. BOX 786
York PA 17405

Dear Sir:

This letter is in response to your February 7, 1996, concerning statistical data for Nitroglycerin Transdermal System. The Office of Generic Drugs (OGD) has reviewed your request and the following comments are provided for your consideration:

1. According to the current policy of the Agency, the deletion of "outliers" on the basis of statistical arguments is not acceptable. There is no direct evidence that subject #121 is really a fast metabolizer and subject #117 is a slow metabolizer, except their plasma drug levels. Moreover, in a two-way crossover, single dose bioequivalence study, each subject will be exposed to both the test and the reference products in a similar manner.

2. Hercon has carried out test for SEX*TREAT and TREAT*GROUP. If these tests are significant, then the study may have serious problems. If they are not significant, then it has been the standard procedure to drop these terms from the statistical model. Failure to drop these terms would result, using PROC GLM, in putting equal weight on the 13 males and 23 females and putting equal weight on the 20 subjects in Group 1 and the 16 subjects in Group 2.

3. In no case ($LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX}), was SEX*TREAT anywhere near significant. However, in the case of trinitroglycerin, there was some borderline evidence of TREAT*GROUP interaction for $LnAUC_{0-T}$ ($p=0.0979$) and $LnAUC_{0-inf}$ ($p=0.0966$) when all subjects are included in the analysis. **Hercon did not do the test for TREAT*GROUP in the case on the 1,2-dinitroglycerin, 1,3-dinitroglycerin** and "All Analytes" analysis (or at least, these tests are not reflected in the ANOVA Tables).

4. Since the dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94), you have to demonstrate that there is no evidence that the difference between the products depends on the group, and for

this reason, you were previously advised to conduct the analysis using the following statistical model:

Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt Trt*Group.

If Trt*Group is not significant (p> 0.10), Trt*Group could be dropped from the model. Then the following model could be used:

Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt;

or, Model Y = Seq Subj(Seq) Per(Group) Trt.

In either case, the period effect should be modeled as Per(Group), and not just Per.

5. Further correspondence regarding this issue must be submitted as an amendment to your application.

The comments provided in this correspondence represent the best advice the Office can provide based on the submitted information, current scientific knowledge, and the proposed issue(s) at hand. The Office reserves the right to modify the bioequivalence testing requirements if needed.

If you have any questions, please call Jason A. Gross, Pharm.D., Consumer Safety Officer at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Deputy Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 89-884 (0.2 mg/hr)
89-885 (0.4 mg/hr)
89-[redacted] (0.6 mg/hr)

NOV 30 1995

Hercon Laboratories Inc.
Attention: Joseph J. Sobecki
P.O. BOX 786
York, PA 17405

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on December 8, 1994, for Nitroglycerin Transdermal Delivery Systems 0.2 mg/hr, 0.4 mg/hr and 0.6 mg/hr.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The bioequivalence study conducted to support approval of these applications has failed to satisfy the appropriate bioequivalence criterion:

   a. For nitroglycerin (TNG) the 90% Ln-transformed confidence intervals for $LnAUC_{0-inf}$ (72; 108) are outside the 80-125% limit.

   b. For 1,3-dinitroglycerin of test product, the 90% Ln-transformed confidence intervals for $LnAUC_{0-T}$ (77; 88), $LnAUC_{0-14}$ (78; 94) and $LnAUC_{0-24}$ (78; 89) are outside the acceptable range of 80-125%.

2. The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94). In order to establish the fact that the differences between the products are not significant in both groups, the analysis should be conducted using the following statistical model:

   Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt Trt*Group.

   If Trt*Group is not significant (p> 0.10), Trt*Group could be dropped from the model. Then the following model could be used:

   Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt;

   or, Model Y = Seq Subj(Seq) Per(Group) Trt.

In either case, the period effect should be modeled as Per(Group), and not just Per. It may be beneficial to try these analyses, since your analysis did not meet the 90% C.I. criterion.

3. Please clarify why *the in vivo* bioequivalence study was conducted in 36 subjects, but reported "40 subjects" in all headings of Tables and Figures in the study report.

4. The residual content data for nitroglycerin in the patches used were not included in the submission.

   This is a redundant deficiency, Hercon was notified in our previous letter dated August 18, 1994, that this data was required.

5. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.4 mg/hr, Lot #M0504NG/556 comparing it to Transderm-Nitro®, 0.4 mg/hr, Lot #C5340 manufactured by Ciba-Geigy is incomplete. The first time point in the release rate data submitted to the Agency is a 30-minute time point, however, the proposed drug release specifications contain 15-minute time point. The appropriate specifications should be established for the release rate of the test product from the data obtained in the drug release study.

6. The drug release data were derived from 6 dosage units of 0.2 mg/hr and 0.6 mg/hr patches. Please be advised that *in vitro* dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range and coefficient of variation data.

   This is a redundant deficiency, Hercon was notified in our previous letter dated August 18, 1994, that this data was required.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be considered major and be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 89-884, 89-885, 89-886

Hercon Laboratories Corporation
Attention: Robert M. Pilson
P.O. Box 786
York, PA 17405

APR 13 1998

Reference Number: Bio 98-088

Dear Sir:

This letter is in response to your correspondence dated March 13, 1998, requesting a reconsideration of the need of skin irritation studies for your Nitroglycerin Transdermal System applications. The Office of Generic Drugs (OGD) has reviewed your request and the following comments are provided for your consideration:

> The skin irritation study submitted in 1993 was conducted prior to the adoption of new standards by the Office of Generic Drugs, requiring studies which compare the test product vs. the reference product. Your application is coming to completion in 1998 when these new standards apply. In the interest of maintaining fairness, the Agency has reviewed information which is available to the Office of Generic Drugs to guide such a decision. The information, which includes adequate product labeling, adequate similarity of transdermal patch components and a skin irritation study demonstrating only mild reactions to the product, is considered adequate to assure the Agency of safety of the test product due to the circumstances outlined above.

If you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

September 11, 1998

Mr. Timothy W. Ames
Project Manager
CDER/OGD/DLPS
Food and Drug Administration, HFD617
Metro Park North 2, Room 113
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
VC

VIA FAX: (301) 443-3839

TELEPHONE AMENDMENT

Re: **ANDA 89-884; Nitroglycerin Transdermal System; (0.2mg/hr)**
ANDA 89-885; Nitroglycerin Transdermal System; (0.4mg/hr)
ANDA 89-886; Nitroglycerin Transdermal System; (0.6mg/hr)

Dear Mr. Ames:

I am writing in response to a telephone call Hercon received on September 10, 1998, from Mr. Ubrani Venkataram of the FDA. Mr. Venkataram informed me that the current FDA practice is to require that each batch of each strength in ANDA submissions for transdermal products be made from separately-produced laminate batches. He noted that the same laminate batch was used to produce the 0.2 mg/hr strength (ANDA 89-884) and the 0.4 mg/hr strength (ANDA 89-885), as described in the batch records provided in our Telephone Amendment dated August 17, 1998. He also informed me that, because Hercon had provided batch records in previous submissions wherein each dosage strength had been produced from separate laminate batches, the FDA would accept the records Hercon has provided. He requested that Hercon provide a Telephone Amendment acknowledging the current FDA practice.

Hercon acknowledges that the FDA requires separately-produced laminate batches for each dose strength. In all future applications, Hercon will provide information demonstrating that each dose strength has been produced from a dedicated laminate batch, as applicable. It is our sincere hope that we have responded satisfactorily to all issues regarding these submissions and look forward to a successful completion of your review of our applications. If you have any additional questions or need additional information, please call me at (717) 764-1191.

Sincerely yours,

Thomas J. Atkins

Thomas J. Atkins, Ph.D.
Vice President
Research and Development
(for Regulatory Affairs)

RECEIVED
SEP 11 1998
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Note: Form 356H and 3 copies to follow via mail.

ORIGINAL

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

August 17, 1998

TELEPHONE AMENDMENT

Mr. Timothy W. Ames
Project Manager
CDER, OGD, DLPS
Metro Park North II
HFD 617
7500 Standish Place
Rockville, Maryland 20855-2773

AC

via Federal Express

Re: **ANDA 89-884; Nitroglycerin Transdermal System; 0.2 mg/hr; 7.0 cm^2**
ANDA 89-885; Nitroglycerin Transdermal System; 0.4 mg/hr; 14.0 cm^2
ANDA 89-886; Nitroglycerin Transdermal System; 0.6 mg/hr; 21.0 cm^2

Dear Mr. Ames:

I am writing in response to your telephone request received on July 31, 1998, regarding the above-referenced ANDA's. During that conference, you asked that Hercon revise the Nitroglycerin Release Rate test in our Manufacturing Controls and in our Stability Program per the sample schedule and acceptance limits stated in the Bioequivalency Comments in Dr. Dale P. Conner's FAX dated June 24, 1998 (copy attached). You also requested that Hercon provide copies of the respective batch records (including the amounts used, and the number of patches produced) for the 0.2 mg/hr and the 0.4 mg/hr batches that were prepared for dose proportionality and stability studies.

The enclosed submission provides copies of the requested changes to our test method and the requested batch records. We are also providing replacement pages to correct clerical/typographical errors found in certain tables in our November submissions. The enclosed submission [three (3) copies] is divided into separate, color-coded, labeled sections for each ANDA. The pages are numbered to correspond to those pages that they replace in our November 1997 Major Amendments. Specifically, this submission contains:

TELEPHONE AMENDMENT

ANDA #89-884

Section	Pages	Description
VI.5	63	Corrected Clerical/Typographical error
VII	65	Corrected Clerical/Typographical error
XII.1	136 - 237	Executed Batch Record for Lot #: L0557NG/614, (0.2 mg/hr)
XV.2	268 - 277	Revised Product Specification including revised Nitroglycerin Release Rate Specification
XVII	307 - 310	Updated Stability Study Data and revised Nitroglycerin Release Rate Specification

ANDA #89-885

Section	Pages	Description
VI.5	63	Corrected Clerical/Typographical error
VII	65	Corrected Clerical/Typographical error
XII.1	135 - 236	Executed Batch Record for Lot #: L0557NG/612, (0.4 mg/hr)
XV.2	267 - 276	Revised Product Specification including revised Nitroglycerin Release Rate Specification
XVII	305 - 308	Updated Stability Study Data and revised Nitroglycerin Release Rate Specification

ANDA #89-886

Section	Pages	Description
VI.5	6193-	Corrected Clerical/Typographical error
XV.2	6398-6400	Revised Product Specification including revised Nitroglycerin Release Rate Specification
XVII	6434-6437	Updated Stability Study Data and revised Nitroglycerin Release Rate Specification

We regret any inconvenience that we may have caused by not providing the executed batch records for the 0.2 mg/hr and the 0.4 mg/hr batches. These records have been thoroughly re-reviewed by Quality Assurance. A summary of the information requested on batch sizes, yields, etc., may be found at the beginning of Section XII.1 for the respective batch records of the 0.2 mg/hr and 0.4 mg/hr products.

Please call me at (717) 764-1191 if you need additional information in regard to this Telephone Amendment.

Sincerely,

Thomas J. Atkins

Thomas J. Atkins, Ph.D.
Vice President - Research & Development
(for Regulatory Affairs)

attachment
enclosures

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

July 9, 1998

Mr. Timothy W. Ames
Sr. Supervisor, Regulatory Affairs
CDER/OGD/DLPS
Food and Drug Administration, HFD617
Metro Park North 2, Room 113
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

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JUL 10
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FACSIMILE AMENDMENT

Re: ANDA 89-884 (0.2mg/hr)
ANDA 89-885 (0.4mg/hr)
ANDA 89-886 (0.6mg/hr)

Dear Mr. Ames:

I am writing in response to a telephone request on July 7, 1998, from Mr. Adolph Vezza regarding the above captioned ANDA's. As an addition to our FACSIMILE AMENDMENT of June 26, 1998, Mr. Vezza requested:

1. Twenty-four (24) additional copies of Final Printed Labeling for the revised Professional Package Insert,

2. Twenty-four (24) additional draft copies of the Patient Package Insert,

3. Twelve (12) copies of the Immediate Patch printing for the 0.2 mg/hr patch (ANDA 89-884), all on one page,

4. Twelve (12) copies of the Immediate Patch printing for the 0.4 mg/hr patch (ANDA 89-885), all on one page, and

5. Twelve (12) copies of the Immediate Patch printing for the 0.6 mg/hr patch (ANDA 89-886), all on one page.

RECEIVED
GENERIC DRUGS

These labeling materials are provided herein under the appropriately marked index tabs.

I believe this complies with Mr. Vezza's phone request. Please call me (717-764-1191) if you need additional information.

Yours truly,

Thomas J. Atkins

Thomas J. Atkins, Ph.D.
Vice President
Research and Development
(for Regulatory Affairs)

Enclosures

cc: Jerry Phillips (Cover Letter Only)
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

\mew

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

June 26, 1998

Mr. Timothy W. Ames
Sr. Supervisor, Regulatory Affairs
CDER/OGD/DLPS
Food and Drug Administration, HFD617
Metro Park North 2, Room 113
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

RECEIVED
JUN 29 [illegible]
GENERIC DRUGS

FACSIMILE AMENDMENT

Re: ANDA 89-884 (0.2mg/hr)
ANDA 89-885 (0.4mg/hr)
~~ANDA 89-886 (0.6mg/hr)~~

Dear Mr. Ames:

I am writing in response to your labeling deficiencies facsimile which we received on April 14, 1998, (copy enclosed) regarding the above captioned ANDA's. I will answer your comments in the order presented, providing a side by side comparison.

1. General Comment

Replace the statement with the symbol "Rx only" throughout your labeling.

We have placed the symbol "Rx only" on our container (pouch), carton (shelf carton), and Professional Package Insert labeling.

2. Immediate Patch

Satisfactory.

3. Container (Pouch) - Patient Instruction No. 6.

ANDA 89-886 (0.6mg/hr) - we have changed to "the remaining piece".

4. Carton.

ANDA 89-884 (0.2mg/hr) - we have changed to "the remaining piece", in Patient Instruction No. 6.

ANDA 89-885 (0.4mg/hr) - we have deleted the word in Patient Instruction No. 4.

5. Professional Package Insert Labeling

Description

We have added the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross linking agent".

Additionally, we are providing 12 copies each of Final Printed Labeling for the appropriately revised Professional Package Insert, Pouch Labeling, and Shelf Carton, as well as 12 copies of the Patient Package Insert in draft form, which has not changed since our submission of November 3, 1997. This labeling is provided in appropriately labeled index tabs.

I believe that we have complied with the requests in your facsimile. Please call me at 717-764-1191 if you need further information.

Sincerely,

Robert M. Pilson,
Director
Regulatory Affairs

Attachments

cc: Jerry Phillips (Cover Letter Only)
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

June 2, 1998

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room E 130
Rockville, MD 20855-2773

AMENDMENT
N / A8

Via Federal Express

Re: Nitroglycerin Transdermal System:

ANDA 89-886 0.6mg/hr; 21 cm2

Dear Dr. Conner:

I am writing in response to two questions conveyed to me by Dr. Nancy Chamberlin in regard to Hercon Laboratories Corporation Major Amendment, November 3, 1997, submitted to the above referenced ANDA 89-886. I have already faxed the answers to these question to Dr. Chamberlin at 301-594-0181. I will answer the questions in the order presented:

1. Biobatch Size: On p. 6267 of the November 3, 1997, submission, cm2 represents the area in square centimeters that was actually coated. On pp. 6360 and 6420, is the theoretical batch size and is directly correlated to the area coated. On p. 6327, represents the expected quantity based on the quantity of laminate and is approximately % of a commercial batch size.

2. Dissolution Conditions: Hercon Test Rev. 1., is enclosed. This is the dissolution method that is referenced on p. 6178 of the November 3, 1997, submission.

I hope this information answers the questions that were raised. Please call me at 717-764-1191 if you need further information.

Sincerely,

Robert M. Pilson

Robert M. Pilson
Director of
Regulatory Affairs

cc: Nancy Chamberlin, Pharm.D.

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JUN 0 3 1998
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HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

labeling review 2/17/98 Douglas Arizzi

November 3, 1997 **MAJOR AMENDMENT**

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

BIOAVAILABILITY
NDA ORIG AMENDMENT 11/6/97
N/AC

via Federal Express

Re: **ANDA 89-884; Nitroglycerin Transdermal System; 0.2 mg/hr; 7.0 cm²**
ANDA 89-885; Nitroglycerin Transdermal System; 0.4 mg/hr; 14.0 cm²
[redacted]

Dear Mr. Sporn:

I am writing in regard to our Major Amendment dated November 4, 1997, (copy of cover letter enclosed), for the above captioned Abbreviated New Drug Applications for Hercon's Nitroglycerin Transdermal System(s). This Major Amendment involves the conduct of a new two treatment, four period, replicate design bioequivalence study comparing Hercon's Nitroglycerin Transdermal System and Summit's Transderm-Nitro®. In this bioequivalence study we have resized our product in the following manner:

ANDA	Strength	Old Size	New Size
ANDA 89-884	0.2 mg/hr	6.75 cm^2	7.0 cm^2
ANDA 89-885	0.4 mg/hr	13.5 cm^2	14.0 cm^2
ANDA 89-886	0.6 mg/hr	20.25 cm^2	21.0 cm^2

Provided herein are the required drug substance manufacturer's and Hercon's Certificates of Analysis for the ingredients utilized in the production of our test product used in our *in vivo* bioequivalence study. An updated Drug Master File ( ) reference letter has been provided by ( ) the drug substance manufacturer of our active ingredient. We have also enclosed analytical reports for the content analysis of our clinical return patches and a comparative dissolution study.

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GENERIC DRUGS

Provided as additional information is a revised Components and Composition table of our product(s) to reflect the new sizes of 7.0 cm^2, 14.0 cm^2 and 21.0 cm^2. Additionally, we

supplying internal documents that have also been updated to reflect the increase in size of the three strengths of our product(s) and include the following:

In a facsimile received from Timothy W. Ames, Project Manager, on July 7, 1997, several labeling deficiencies were noted. I will respond to these in the order presented in a side by side manner:

1. Container (pouch)

   a. ***We encourage you to differentiate the different strengths of container labels by using contrasting colors and/or boxing.***

      We are unable to comply with this request at this time due to the intricacies involved with our distributors' container labels of contrasting colors and/or boxing.

b. ***Relocate the established name, to appear at the top of the front panel prior to the rate of release and the size of the system.***

We have relocated the established name, as requested.

c. ***Print "in vivo" in lowercase italic print.***

We have complied by printing in lower case italics.

d ***Each system ____ cm^2 contains ____ mg of nitroglycerin in acrylic-based polymer adhesive with a cross-linking agent.***

We have revised the text as requested.

e. Patient Instructions

i. ***To be consistent with your Patient Package Insert revise patient instruction # 4 to read as follows:***

Hold patch by the smaller part of the backing (which is still in place) to avoid touching the sticky side of the patch. Apply the sticky side of the patch to your skin. Smooth down.

We have added the requested text.

ii. ***If space permits revise patient instruction # 6 to be consistent with your Patient Package Insert, "...in place. Then wash your hands with soap and water to remove any drug residue."***

We have added the requested text.

iii. ***Add the statement "APPLY IMMEDIATELY UPON REMOVAL FROM POUCH", at the end of patient instruction # 6.***

We have added the requested text after the storage conditions.

iv. ***We encourage you to add the statement "Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval; unless otherwise directed by your physician", following patient instruction # 6.***